Author's response to reviews

Title: Safety and Effectiveness of Adalimumab in a Clinical Setting that Reflects Canadian Standard of Care for the Treatment of Rheumatoid Arthritis (RA): Results from the CanAct Study

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Author's response to reviews: see over
We thank the reviewers for their helpful comments. Below, please find our responses (italicized) to specific comments:

Reviewer #1, Bernhard Manger

Solid data in a large cohort, confirming data, which are already well known and accepted.

No specific comments to address.

Reviewer #2, Rudolf Puchner

This large observational study reflects the efficacy of Biologics under conditions of routine clinical care. The data approve the already well investigated effectiveness and tolerability of adalimumab in real world clinical practice. It is of interest and comforting to know that the safety profile of adalimumab is similar to previously published trials. The reported low rate of serious infections is a matter of concern but should be further investigated over a longer period.

Indeed, we agree with the reviewer that the low rate of serious infection observed in the present study may reflect the short duration of the study (12 weeks) and have commented as such in the Discussion section.

Due to the large number of patients the study is of interest for practising rheumatologists. In this study the vast majority of patients was first treated with a biologic agent after a long period of illness-the mean disease duration since diagnosis was 12.5 years (27.5% of patients that received prior BDMARD therapy included). It would be of interest to comment on this point.

This level of disease duration at baseline is consistent with the access to care in Canada at the time the study was conducted. Further, this duration is not that different from biological DMARD registry data observed in European and American databases. We have added statements to this effect in the Discussion section.

Reviewer #3, Editor

This paper deals with the administration of ADA under more or less routine conditions. As it stands at the moment it does not provide additional information to all the other reports about anti-TNF-agents. However, from the viewpoint of a practicing rheumatologist it underlines the effectiveness and also the tolerability consideration with respect to anti-TNF agents, in this case ADA. There could be a possibility to increase the interest in the paper by giving information about the fate of the non-responders, e.g. providing figures with the percentage of reponders acc. to the ACR criteria, but also the patients not achieving a response or experiencing worsening of the disease. This may help to estimate the likelihood of success for the individual patient better than bars stopping at a certain percent level and neglecting the fact of non-response.
It is well-understood that the proportion of patients failing to demonstrate an ACR response is the inverse proportion of ACR20 responders, given that ACR50 and ACR70 responders also satisfy the ACR20 response criteria. Given the complexity of the ACR response criteria, it is difficult to assess the proportion of patients who demonstrate a worsening of the disease, as there is no standard definition in the literature. To address this comment, we have looked at a mean level at the change and % change from baseline to Week 12 in ACR core components in ACR20 non-responders. The data indicate that statistically significant reductions in some ACR core components were observed for ACR20 non-responders. Indeed, several of the response measures achieved >20% improvement at a mean level. However, other parameters, such as the patient-reported outcomes, did not show >20% improvement or even worsened at a mean level over the 12 weeks of the study in these patients. We have provided these data in a new table (Table 3) and discussed these data in the text of the Results section.

It would also give an opportunity to enhance the clarity by reporting about the patients treated for 24 weeks and give the rate of patients initially partially responding, but finally not responding.

Indeed, this is an excellent suggestion by the editor, and it is one that we are actively pursuing for a separate publication. Given the complexity of this analysis coupled with the fact that this manuscript has only addressed the first 12 weeks of this study, we feel as though this information should be left for a subsequent publication.